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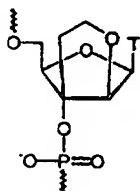
## Published

With international search report.

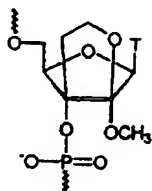
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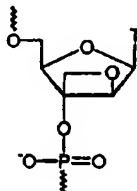
(54) Title: BI- AND TRI-CYCLIC NUCLEOSIDE, NUCLEOTIDE AND OLIGONUCLEOTIDE ANALOGUES



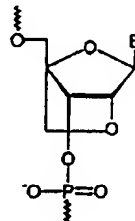
V



X



Y



ZT: B = thymine-1-yl  
ZU: B = uracil-1-yl  
ZG: B = guanine-9-yl  
ZC: B = cytosine-1-yl  
ZA: B = adenine-9-yl  
ZMeC: B = 5-methylcytosine-1-yl

## (57) Abstract

The present invention relates to novel bicyclic and tricyclic nucleoside and nucleotide analogues of formula (I) as well as to oligonucleotides comprising such elements. The nucleotide analogues, LNAs (Locked Nucleoside Analogues), are able to provide valuable improvements to oligonucleotides with respect to affinity and specificity towards complementary RNA and DNA oligomers. The novel type of LNA modified oligonucleotides, as well as the LNAs as such, are useful in a wide range of diagnostic applications as well as therapeutic applications. Among these can be mentioned antisense applications, PCR applications, strand displacement oligomers, as substrates for nucleic acid polymerases, as nucleotide based drugs, etc. The present invention also relates to such applications.

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# INTERNATIONAL SEARCH REPORT

|   |  |
|---|--|
| International Application No<br>PCT/DK 98/00393   |  |
| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>IPC 6 C07H19/04 C07H21/00 A61K31/70 C12Q1/68  |  |
| According to International Patent Classification (IPC) or to both national classification and IPC   |  |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>IPC 6 C07H A61K C12Q  |  |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched   |  |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used)  |  |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>   |  |
| Category *  | Citation of document, with indication, where appropriate, of the relevant passages<br>Relevant to claim No.  |
| Y   | P.NIELSEN ET AL.: "A Novel Class of Conformationally Restricted Oligonucleotide Analogues : Synthesis of 2',3'-Bridged Monomers and RNA-Selective Hybridisation."<br>JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS.,<br>no. 9, 7 May 1997, LETCHWORTH GB,<br>pages 825-826, XP002046993<br>cited in the application<br>see page 825, compounds 5 and x<br>---<br>-/-- |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input type="checkbox"/> Patent family members are listed in annex.  |  |
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| Date of the actual completion of the international search<br>8 March 1999   | Date of mailing of the international search report<br>06. 05. 1999   |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016  | Authorized officer<br>SCOTT, J   |

# INTERNATIONAL SEARCH REPORT

Int. onal Application No

PCT/DK 98/00393

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| Y          | V.E.MARQUEZ ET AL.: "Nucleosides with a Twist. Can Fixed Forms of Sugar Ring Pucker Influence Biological Activity in Nucleosides and Oligonucleotides ?" JOURNAL OF MEDICINAL CHEMISTRY., vol. 39, no. 19, 13 September 1996, WASHINGTON US, pages 3739-3747, XP002094300 see the whole document<br>---          | 1-75,<br>80-140       |
| Y          | M.BOLLI ET AL.: "Bicyclo-DNA : A Hoogsteen-Selective Pairing System." CHEMISTRY AND BIOLOGY, no. 3, March 1996, pages 197-206, XP002094301 see the whole document<br>---   | 1-75,<br>80-140       |
| A          | C.G.YANNOPOULOS ET AL.: "2',3'-Cyclopropanated Nucleoside Dimers." SYNLETT., no. 4, 1997, STUTTGART DE, pages 378-380, XP002046994 cited in the application see the whole document<br>---  | 1                     |
| A          | CHEMICAL ABSTRACTS, vol. 70, no. 1, 6 January 1969 Columbus, Ohio, US; abstract no. 3737b, G.ZIGEUNER ET AL.: "Heterocycles. XVI. 1,4-Dimethyl-3-acetoxy-7-acetamido-2-oxabi cyclo(2.2.1)heptane." page 343; column 1; XP002046995 see abstract & MONATSCH. CHEM., vol. 99, no. 5, 1968, pages 2111-2120,<br>--- | 1                     |
| P,X        | R.KUMAR ET AL.: "The first Analogues of LNA (Locked Nucleic Acids) : Phosphorothioate-LNA and 2'-Thio-LNA." BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, no. 8, 1998, pages 2219-2222, XP002094302 see the whole document<br>---  | 1-75,<br>80-140       |

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 98/00393

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| P,X        | S.K.SINGH ET AL.: "LNA (Locked Nucleic Acids) : Synthesis and High-Affinity Nucleic Acid Recognition."<br>CHEMICAL COMMUNICATIONS.,<br>no. 4, 21 February 1998, CIETY OF CHEMISTRY GB,<br>pages 455-456, XP002094303<br>see the whole document<br>---  | 1-75,<br>80-140       |
| P,X        | A.A.KOSHKIN ET AL.: "LNA (Locked Nucleic Acids) : Synthesis of the Adenine, Cytosine, Guanine, 5-Methylcytosine, Thymine and Uracil Bicyclonucleoside Monomers, Oligomerisation, and the Unprecedented Nucleic Acid Recognition."<br>TETRAHEDRON,<br>vol. 54, 1998,<br>pages 3607-3630, XP002094304<br>see the whole document<br>--- | 1-75,<br>80-140       |
| T          | P.HERDEWIJN: "Targeting RNA with Conformationally Restricted Oligonucleotides."<br>LIEBIGS ANNALEN: ORGANIC AND BIOORGANIC CHEMISTRY.,<br>no. 9, September 1996, ISHERS US,<br>pages 1337-1348, XP002094305<br>see the whole document<br>-----   | 1                     |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK 98/00393

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-75, 80-140 partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-75,80-140 partially

A nucleoside with one pair of geminal substituents forming a biradical between the 2' and 4'positions (LNA); oligomers containing these LNAs; uses of both the LNA and the oligomer containing the LNA; conjugates of the oligomer; solid surfaces with LNA or oligomers containing them.

2. Claims: 1-28,43-68,76-82,93-140 partially

A nucleoside with one pair of geminal substituents forming a biradical between the 2' and 3'positions (LNA); oligomers containing these LNAs; uses of both the LNA and the oligomer containing the LNA; conjugates of the oligomer; solid surfaces with LNA or oligomers containing them.

3. Claims: 1-28,43-68,93-140 partially

A nucleoside with one pair of geminal substituents forming a biradical between the 3' and 4'positions (LNA); oligomers containing these LNAs; uses of both the LNA and the oligomer containing the LNA; conjugates of the oligomer; solid surfaces with LNA or oligomers containing them.

4. Claims: 1-28,43-68,93-140 partially

A nucleoside with one pair of geminal substituents forming a biradical between the 3' and 5'positions (LNA); oligomers containing these LNAs; uses of both the LNA and the oligomer containing the LNA; conjugates of the oligomer; solid surfaces with LNA or oligomers containing them.

5. Claims: 1-28,43-68,93-140 partially

A nucleoside with one pair of geminal substituents forming a biradical between the 1' and 4'positions (LNA); oligomers containing these LNAs; uses of both the LNA and the oligomer containing the LNA; conjugates of the oligomer; solid surfaces with LNA or oligomers containing them.

6. Claims: 1-28,43-68,93-140 partially

A nucleoside with one pair of geminal substituents forming a biradical between the 1' and 2'positions (LNA); oligomers containing these LNAs; uses of both the LNA and the oligomer containing the LNA; conjugates of the oligomer; solid surfaces with LNA or oligomers containing them.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. Claims: 1-140 partially

A nucleoside with two pairs of geminal substituents forming a biradical (LNA); oligomers containing these LNAs; uses of both the LNA and the oligomer containing the LNA; conjugates of the oligomer; solid surfaces with LNA or oligomers containing them.

8. Claims: 1-11,39-59,97,103,105-140 partially

Oligomers containing LNAs with one pair of geminal substituents forming a biradical between the 1' and 5' positions; uses of both the LNA and the oligomer containing the LNA; conjugates of the oligomer; solid surfaces with LNA or oligomers containing them.

9. Claims: 1-11,39-59,97,103,105-140 partially

Oligomers containing LNAs with one pair of geminal substituents forming a biradical between the 1' and 3' positions; uses of both the LNA and the oligomer containing the LNA; conjugates of the oligomer; solid surfaces with LNA or oligomers containing them.

10. Claims: 1-11,39-59,97,103,105-140 partially

Oligomers containing LNAs with one pair of geminal substituents forming a biradical between the 2' and 5' positions; uses of both the LNA and the oligomer containing the LNA; conjugates of the oligomer; solid surfaces with LNA or oligomers containing them.

11. Claims: 1-11,39-59,97,103,105-140 partially

Oligomers containing these LNAs with one pair of geminal substituents forming a biradical between the 4' and 5' positions; uses of both the LNA and the oligomer containing the LNA; conjugates of the oligomer; solid surfaces with LNA or oligomers containing them.